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Efficacy of Tenapanor in Patients With Irritable Bowel Syndrome With Constipation (IBS-C): A Post Hoc Analysis of Patients With and Without Prior Use of Other IBS-C Prescription Medications From the Phase 3 T3MPO-1 and T3MPO-2 Studies

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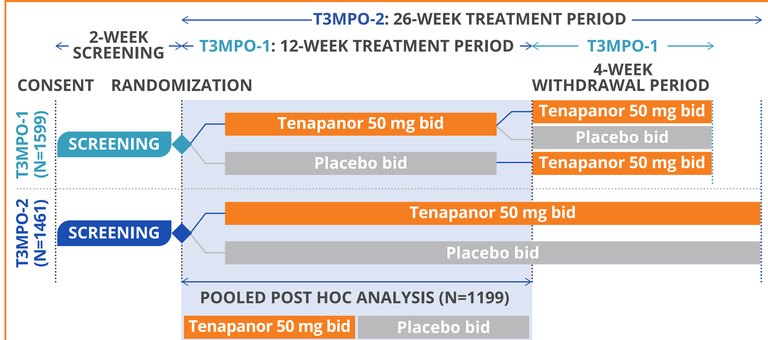
Introduction

- Tenapanor is a first-in-class, minimally absorbed, small-molecule inhibitor of intestinal sodium/hydrogen exchanger isoform 3 (NHE3) approved by the Food and Drug Administration (FDA) for the treatment of IBS-C in adults.[1,2]
- Through NHE3 inhibition, tenapanor reduces the absorption of sodium and retains water content in the gut, leading to softer stool consistency and accelerated transit.[3-5]
- Tenapanor may also decrease visceral hypersensitivity and intestinal permeability to macromolecules, mast cells, and mast cell mediators, leading to less abdominal pain in patients with IBS-C.[6]
- Two multicenter, phase 3, randomized, double-blind, placebo-controlled clinical trials, T3MPO-1 (NCT02621892) and T3MPO-2 (NCT02686138), showed patients treated with tenapanor 50 mg twice a day (bid) experienced both significant increases in complete spontaneous bowel movements (CSBMs) and decreases in abdominal pain compared with those receiving placebo.[7,8]
- A small percentage of patients enrolled into T3MPO-1 and T3MPO-2 reported prior use of prescription drugs, including linaclotide and lubiprostone, for the treatment of IBS-C.
- Here, we conducted a post hoc analysis of data pooled from T3MPO-1 and T3MPO-2 to assess whether prior use of prescription medications affected clinical response to tenapanor.

Methods

- Study methods for the phase 3 studies have been described previously.[7,8] To summarize, adults with IBS-C were randomized to tenapanor (50 mg bid) or placebo for 12- and 26-week treatment periods in T3MPO-1 and T3MPO-2, respectively (**Figure 1**).

Figure 1: Study Design[a]



[a]The association between treatment (tenapanor and placebo) was assessed using the Cochran– Mantel–Haenszel (CMH) test. The CMH *P* value was based on a 1 degree of freedom test for association between treatment (tenapanor and placebo), stratified by the pooled investigator site.
bid, twice a day.

- The trials' designs allowed patients who had history of IBS-C prescription drug use to enroll, as long as they stopped taking other IBS-C prescription medications during the screening period and the treatment period of the studies.
- We evaluated responder rates in tenapanor-treated patients with and without prior use of other FDA-approved IBS-C prescription medication.
  - The FDA composite endpoint responder was a patient who had both a CSBM response and an abdominal pain response in the same week for ≥6 of the first 12 treatment weeks (6 of 12–week combined responder).
    - CSBM response was defined as an increase of ≥1 weekly CSBM from baseline.
    - An abdominal pain response was defined as a ≥30% decrease in average weekly worst abdominal pain from baseline.

Results

Patients

- The pooled intent-to-treat analysis set included 600 tenapanor-treated patients and 599 patients receiving placebo.
- Among the patients receiving tenapanor, 26 (4.3%) reported prior IBS-C prescription medication use: 16 were treated with linaclotide alone, and 10 with lubiprostone alone (**Table 1**).
- Among the patients receiving placebo, 32 (5.3%) reported prior IBS-C prescription medication use: 19 were treated with linaclotide alone, 12 with lubiprostone alone, and 1 reported a history of taking both linaclotide and lubiprostone (**Table 1**).
- The demographics and baseline characteristics were generally well balanced among the patients without prior prescription medication use; however, differences were observed between the patients receiving tenapanor or placebo among the patients with prior prescription medication use, which may be attributed to the small percentage of the population with prior medication use (**Table 1**).

Table 1: Patient Demographics and Baseline Characteristics of Patients With and Without Prior IBS-C Prescription Medication Use Based on Pooled Data From the T3MPO-1 and T3MPO-2 Studies (Intent-to-Treat Analysis Set)

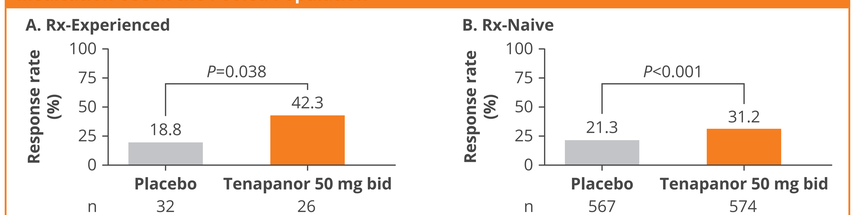
	Prior IBS-C prescription medication use		No prior IBS-C prescription medication use	
Demographic/characteristic	**Tenapanor (N=26)**	**Placebo (N=32)**	**Tenapanor (N=576)**	**Placebo (N=569)**
Age (years)	47.6 (15.3)	49.6 (12.8)	45.4 (13.2)	44.6 (13.4)
Sex, n (%)				
Female	19 (73.1)	27 (84.4)	466 (80.9)	471 (82.8)
Race, n (%)				
White	21 (80.8)	20 (62.5)	366 (63.5)	360 (63.3)
African American	2 (7.7)	11 (34.4)	179 (31.1)	181 (31.8)
Asian	3 (11.5)	0 (0.0)	19 (3.3)	13 (2.3)
Other[a]	0 (0.0)	1 (3.1)	12 (2.1)	15 (2.6)
Body mass index, kg/m²	28.1 (4.5)	32.2 (6.5)	30.3 (7.3)	30.0 (6.9)
Duration of IBS symptoms before randomization, years	9.7 (12.5)	8.8 (9.9)	10.9 (11.3)[b]	11.3 (11.6)[b]
Disease characteristic				
Abdominal pain[c]	5.8 (1.2)	5.7 (1.6)	6.3 (1.7)	6.3 (1.7)
CSBMs per week[d]	0.2 (0.4)	0.2 (0.4)	0.2 (0.6)	0.2 (0.4)
Prior FDA-approved IBS-C prescription medication used, n (%)				
Linaclotide	16 (61.5)	19 (59.4)	NA	NA
Lubiprostone	10 (38.5)	12 (37.5)	NA	NA
Linaclotide and Lubiprostone	0 (0.0)	1 (3.1)	NA	NA

Data are shown as mean (SD) unless otherwise stated.
[a]Includes American Indian or Alaskan Native, multiple, and unknown. [b]Duration of IBS symptoms before randomization reported for n=574 receiving tenapanor and n=565 receiving placebo. [c]Assessed daily using a 0–10-point scale, where 0 = none and 10 = very severe; the average weekly score was calculated from scores for all days during a week with ≥4 recorded diary days. [d]Data are shown as mean (SD) of the average of the weekly scores during the screening period for individual patients.
CSBM, complete spontaneous bowel movement; FDA, Food and Drug Administration; IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome with constipation; NA, not applicable.

Response Rates

- Among patients with prior IBS-C prescription medication use, the composite response rate in tenapanor-treated patients was higher than that in placebo-treated patients (*P*=0.038) (**Figure 2A**).
- Similarly, among patients without prior use of IBS-C prescription medication, the composite response rate was higher in tenapanor-treated patients than in placebo-treated patients (*P*<0.001) (**Figure 2B**).

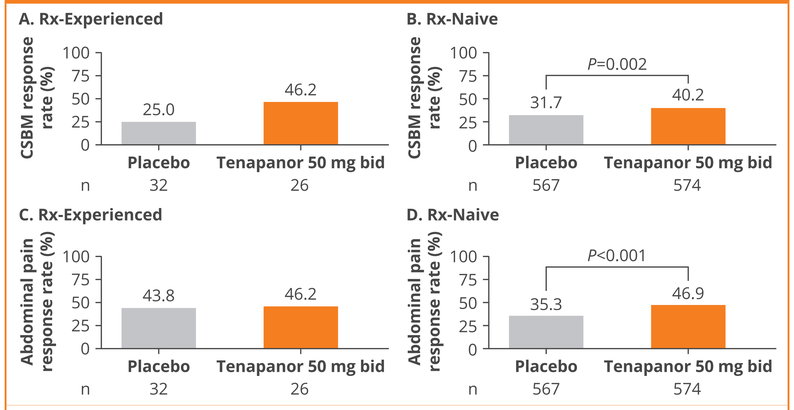
Figure 2: Composite Response Rates in Patients With (A) and Without (B) Prior IBS-C Prescription Medication Use in the Pooled Population[a,b]



[a]The composite response is defined as achieving both a CSBM response and an abdominal pain response in the same week for ≥6 of the first 12 treatment weeks (6 of 12–week combined responder).
[b]With a small sample size (n=58), the Rx-Experienced subgroup still achieved statistical significance in the treatment comparison of the composite response endpoint, with a *P* value of 0.038.
bid, twice a day; CSBM, complete spontaneous bowel movement; IBS-C, irritable bowel syndrome with constipation; Rx, treatment.

- Among patients with prior IBS-C prescription medication use, the CSBM response rate in tenapanor-treated patients was higher than that in placebo-treated patients (**Figure 3A**).
- Among patients without prior IBS-C prescription medication use, the CSBM response rate in tenapanor-treated patients was higher than that in placebo-treated patients (*P*=0.002) (**Figure 3B**).
- Among patients with prior IBS-C prescription medication use, the abdominal pain response rate in tenapanor-treated patients was similar to that of placebo-treated patients (**Figure 3C**).
- Among patients without prior use of IBS-C prescription medication, the abdominal response rate in tenapanor-treated patients was higher than that in placebo-treated patients (*P*<0.001) (**Figure 3D**).

Figure 3: CSBM and Abdominal Pain Response Rates in Patients With (A, C) and Without (B, D) Prior IBS-C Prescription Medication Use in the Pooled Population From T3MPO-1 and T3MPO-2 Studies[a,b,c]



[a]A CSBM responder was defined as a patient with an increase of ≥1 weekly CSBM from baseline. [b]The sample size of the subgroup of patients with prior IBS-C prescription medication use (Rx-Experienced; n=58) was too small to yield a statistically significant *P* value for the treatment comparison of the CSBM response endpoint. [c]An abdominal pain responder is defined as a patient with ≥30% decrease in average weekly worst abdominal pain from baseline.
bid, twice a day; CSBM, complete spontaneous bowel movement; IBS-C, irritable bowel syndrome with constipation; Rx, treatment.

Safety

- Safety outcomes in T3MPO-1 and T3MPO-2 have been previously reported. Tenapanor was generally well tolerated with an acceptable safety profile.[7,8]
- Treatment-emergent adverse events (TEAEs) were reported by 59% of patients with prior IBS-C prescription medication use, and by 36% of patients without prior IBS-C prescription medication use (**Table 2**).
- The most common TEAE during the randomized treatment period was diarrhea, both in patients with (26.9%) and without (14.8%) prior IBS-C medication use (**Table 2**).

Table 2: Treatment-Emergent Adverse Events Reported by Patients With and Without Prior IBS-C Prescription Medication Use (Safety Analysis Set)

	Prior IBS-C prescription medication use[a]		No prior IBS-C prescription medication use	
n (%)	**Tenapanor (N=26)**	**Placebo (N=32)**	**Tenapanor (N=576)**	**Placebo (N=569)**
Patients with any TEAE, n (%)	14 (53.8)	20 (62.5)	239 (41.5)	178 (31.3)
TEAEs experienced by ≥3% patients				
Diarrhea	7 (26.9)	3 (9.4)	85 (14.8)	13 (2.3)
Abdominal pain	3 (11.5)	2 (6.3)	5 (0.9)	10 (1.8)
Nausea	1 (3.8)	4 (12.5)	15 (2.6)	12 (2.1)
Nasopharyngitis	0	3 (9.4)	18 (3.1)	13 (2.3)
Abdominal pain upper	0	2 (6.3)	0	2 (0.4)
Vomiting	0	2 (6.3)	8 (1.4)	11 (1.9)
Bursitis	2 (7.7)	0	0	1 (0.2)
Headache	0	2 (6.3)	8 (1.4)	10 (1.8)
Insomnia	2 (7.7)	0	1 (0.2)	0
Asthma	0	2 (6.3)	2 (0.3)	1 (0.2)
Urinary tract infection	-	-	9 (1.6)	19 (3.3)

Data are n (%).
[a]Numeric differences between prior medication subgroups and treatment arms could be due to the small sample size of the subgroup of patients with prior IBS-C medication use.
-, not reported; IBS-C, irritable bowel syndrome with constipation; TEAE, treatment-emergent adverse event.

Conclusions

In the T3MPO-1 and T3MPO-2 clinical trials, treatment with tenapanor improved CSBMs and abdominal pain among adults with IBS-C regardless of prior IBS-C prescription medication use.

Overall, tenapanor demonstrated an acceptable safety and tolerability profile.

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Disclosures

Eric Shah has served as a consultant for Salix Pharmaceuticals. Brian Lacy is a consultant for Allakos, Allergan, Arena, Cosmos, Ironwood, Salix, and Viver. Yang Yang, Suling Zhao, Laura Williams, Susan Edelstein, and David Rosenbaum are employees of Ardelyx, Inc.

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